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# How cells die determines whether immune system mounts response

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Every moment we live, cells in our bodies are dying. One type of cell death activates an immune response while another type doesn't. Now researchers at Washington University School of Medicine in St. Louis and St. Jude's Children's Research Hospital in Memphis have figured out how some dying cells signal the immune system. They say the finding eventually could have important implications in the treatment of autoimmune diseases and cancer.

In the July 18 issue of the journal *Immunity,* the researchers report a molecule, called high mobility group box-1 protein (HMGB1), which cells release when they die, seems to determine whether the immune system is alerted. But what happens to HMGB1 after it's made and whether the immune system ever gets the signal depends on how the cell dies.

"Cells die in two general ways: apoptosis, or programmed cell death, and necrosis, which results from injuries and infections," says Thomas A. Ferguson, Ph.D., a senior investigator on the study and professor of ophthalmology and visual sciences at Washington University. "In general, we don't want the immune system to respond to apoptosis, but we do want an immune response following necrosis because necrotic death can be a sign of infection. Necrotic cells release components to stimulate the immune system, and one is the HMGB1molecule."

Apoptosis normally is a healthy process that occurs all the time, so it shouldn't activate an immune response, according to co-senior

investigator Douglas R. Green, Ph.D. the Peter C. Doherty Endowed Professor of Immunology at St. Jude's.

"Apoptosis is an orderly death that occurs during development and tissue turnover, and it's an important process that allows us to replace old, worn-out cells with fresh, new ones," says Green. "We don't need the immune system paying attention as our cells die through apoptosis. When it does react to apoptosis, we can develop autoimmunity, as in diabetes, arthritis and other autoimmune diseases in which the immune system will attack the 'self.'"

The researchers say scientists had believed that necrotic cells released HMGB1 whereas apoptotic cells did not. The problem is that experiments in Ferguson's laboratory and elsewhere have found that in some cases, apoptotic cells also release the HMGB1 protein.

"Whether they were apoptotic or necrotic, we found that dying cells were releasing the protein, but the cells that were undergoing apoptosis still weren't stimulating the immune system," Ferguson says. "So our question was, 'If the molecule being released is the same, why is it stimulating the immune system in one situation and not in another?'"

Further experiments showed that when they die, apoptotic cells also produce free radicals, and those reactive oxygen free radicals modify HMGB1 to prevent it from stimulating the immune system. In necrosis, no free radicals are produced, so HMGB1 both signals and stimulates an immune system response.

Free radicals have been thought to be bad for us, but in the case of cell death, they have the beneficial effect of preventing the immune system from attacking and destroying healthy cells. The finding may have important implications, both for some autoimmune processes and for cancer treatment. The researchers believe it may be possible to use

HMGB1 to stoke up the immune system in response to cancer.

"Sometimes tumors can stimulate an immune response," says Green. "This study suggests that when we give chemotherapy, whether dying tumor cells make these reactive oxygen free radicals could be very important because if we can mount an immune response to the tumor, chemotherapy might be more successful, and we may be able to keep the cancer from coming back."

The inverse would be true in autoimmune diseases.

"If we could oxidize the danger signals coming from dying cells in a way similar to how apoptotic cells release free radicals to modify HMGB1, maybe autoimmunity could be down-regulated," Ferguson says.

Source: Washington University School of Medicine

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